Effects of Amlodipine on Baroreflex and Sympathetic Nervous System Activity in Mild-to-Moderate Hypertension

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To investigate the effect of amlodipine on baroreflex sensitivity and sympathetic system activity, 36 patients with essential hypertension were randomized to once-daily, double-blind treatment with amlodipine 5 mg or placebo 5 mg for 60 days. Measurements with a Finapres device allowed calculation of baroreflex sensitivity and blood pressure (BP) variability. Adrenergic activity was assessed via measurements of lymphocyte β2-adrenoceptors and plasma catecholamine concentrations. Compared with placebo, amlodipine significantly decreased BP, but did not significantly alter baroreflex sensitivity. Spectral analysis of Finapres data showed that, compared with placebo, amlodipine decreased the variability of systolic blood pressure, diastolic blood pressure, and RR interval in the low frequency band. There were no simultaneous changes in adrenergic function, however, suggesting that these effects of amlodipine were not mediated via sympathetic nervous system activation. Am J Hypertens 2001;14:424–428 © 2001 American Journal of Hypertension, Ltd.

Key Words: Amlodipine, baroreflex sensitivity, blood pressure variability, hypertension, sympathetic nervous system.

Sympathetic nervous system activity is increased in patients with essential hypertension, possibly as a result of a decrease in the sensitivity of their arterial baroreflex.1 Increased sympathetic activity can lead to left ventricular hypertrophy and to the development and progression of atherosclerosis.2 Baroreflex regulation of heart rate also contributes to the spontaneous control of blood pressure (BP) at rest,3 and impaired baroreflex sensitivity can therefore increase BP variability in hypertensive subjects.

Treatment with rapidly absorbed, short-acting dihydropyridines can increase sympathetic activity. The abrupt drop in BP produced by these agents can trigger arterial baroreflex-mediated stimulation of the sympathetic nervous system, resulting in reflex tachycardia.4 Repeated dosing with these agents during chronic treatment may lead to sustained acute sympathetic activity that, in turn, can result in myocardial ischemia, ventricular arrhythmias, and potentially death in patients with coronary artery disease. These risks may be circumvented by treatment with long-acting dihydropyridines such as amlodipine, which exhibit a gradual and sustained antihypertensive effect with no sudden dose-related fluctuations in BP.5

The current study was designed to investigate the effects of amlodipine on BP and heart rate variability, baroreflex sensitivity, and sympathetic nervous system activity in patients with mild-to-moderate hypertension.

Methods

Patients

A total of 36 patients (men and women), aged 18 to 70 years, with mild-to-moderate essential hypertension (diastolic blood pressure [DBP] 96 to 114 mm Hg and/or systolic blood pressure [SBP] 160 to 210 mm Hg) were eligible for inclusion. Major exclusion criteria included secondary, severe, or malignant hypertension (DBP > 114 mm Hg and/or SBP > 210 mm Hg); hypotension (SBP < 100 mm Hg); noncompensated or poorly controlled heart failure; left ventricular mass index > 130 g/m²; and unstable angina or myocardial infarction in the preceding 3 months.
Design
This was a 90-day randomized, double-blind, placebo-controlled, parallel group trial consisting of a screening phase (day −30 to day 0) and a treatment phase (day 0 to day 60). All patients received placebo during the screening phase and, at day 0, eligible patients were randomized to once-daily treatment with either amlodipine 5 mg or placebo. The dose was doubled on day 30 if DBP was 90 to 114 mmHg. Clinical evaluations were performed in the fasted state on day −30, day 0, day 30, and day 60.

Recordings Using Finapres Method
Continuous blood pressure was recorded over a 45-min period on days 0 and 60, noninvasively, using a finger plethysmographic device (Finapres) (Finapres 2300tm, Ohmeda BOC Inc, USA). From these measurements, a specifically designed computer program determined SBP, DBP, and heart rate on a beat-to-beat basis (M. Comparat ISN-UJF, CNRS, France).

Variability in each frequency domain was evaluated by spectral analysis using a modified fast Fourier transform (FFT) over a 512 time-series. A mean periodogram was calculated to limit the fluctuations in the spectral estimation. Three principal bands were measured: very low frequency (VLF) (0.005 to 0.05 Hz); low frequency (LF) (0.05 to 0.14 Hz), and high frequency (HF) (0.14 to 0.4 Hz).

The cardiac baroreflex loop in the LF band was evaluated using cross spectral analysis. From these frequency points, only those with a coherence > 0.7 were selected to compute the mean modulus value in this band. The cardiac baroreflex sensitivity was also examined using the method previously described by Parati et al.

Blood Pressure Measurements
The DBP, SBP, and heart rate were measured at each clinic visit under standard resting conditions using a conventional mercury sphygmomanometer. The mean of three readings taken at intervals of 3 min was recorded.

The ABPM was conducted on days 0 and 60 with a noninvasive automated device9 that recorded SBP, DBP, and heart rate every 15 min over 24 h. Hourly means over the daytime (07:00 to 22:00) and nighttime (22:00 to 07:00) were calculated for SBP, DBP, and heart rate. Individual peak effect for blood pressure was identified as the greatest placebo-adjusted difference in mean blood pressure over 6 consecutive h (measured 1 to 12 h after dosing). Patients with a decrease in peak effect of 5 mm Hg for DBP and 10 mm Hg for SBP between days 0 and 60 were considered to be responders.

Measurement of Adrenergic Activity
Regional cardiac sympathetic activity was assessed by measuring lymphocyte β2-adrenoceptor density on circulating lymphocytes, which is increased in hypertension and correlates with changes in cardiac β2-adrenoceptors. Lymphocyte β2-adrenoceptors were measured on days 0 and 60. Purified lymphocytes from fasted blood samples were added to incubation medium containing H-CGP12177 (specific activity 43 Ci/mmoles) to a final volume of 500 μL. Concentrations of 0.25 to 9.0 mmoles/L H-CGP12177 were used in saturation studies, with each experiment conducted in triplicate. Nonspecific binding was determined under the same conditions in the presence of (−)propranolol. The number of binding sites and the dissociation constant were calculated by Scatchard analysis.

Plasma concentrations of norepinephrine, epinephrine, and dopamine were assayed on days 0 and 60 according to the method of Da Prada and Zurcher.

Safety Evaluation
The nature, duration, severity, outcome, and causal relationship with study treatment were recorded for all adverse events that occurred during the trial.

Statistical Analysis
An intent-to-treat statistical analysis was performed. The normality of distributions of the various parameters was investigated using the Shapiro and Wilk test and by determination of the coefficients of kurtosis and skewness. Parameters not following a normal distribution were compared using the Mann-Whitney nonparametric test for quantitative ordinal variables. Dichotomous variables were compared using Fisher’s exact probability test. P ≤ .05 was considered statistically significant, and all comparisons were bilateral. Results were expressed as the mean ± SD for parameters with a normal distribution, and as the median with first and third quartiles for those with a nonnormal distribution.

Results
Study Populations
A total of 36 patients were randomized to treatment with amlodipine 5 mg (n = 18) and placebo (n = 18). Treatment groups were well matched with respect to baseline characteristics. Laboratory parameters were also comparable between treatment groups.

Four patients in the amlodipine group withdrew from the study: one for treatment inefficacy and two for adverse events (leg edema and facial flushing), and one patient requested withdrawal. One patient in the placebo group discontinued the study because of difficulties in clinic attendance. Therefore, 31 patients completed the study.

The daily dose was adjusted on day 30 in 11 patients in each treatment group, such that the mean daily dosage at the end of the study was 8.1 ± 2.5 mg/day in both groups.

Blood Pressure and Heart Rate Measurements
Mean ABPM measurements for SBP and DBP were comparable in the two treatment groups at day 0. However,
patients receiving amlodipine had a significantly greater decrease in these values at day 60, compared with placebo, for all periods investigated (24-h, daytime, and night-time; \( P < .005 \)). There were no significant differences between the treatment groups with respect to heart rate at day 0 or day 60, or the change from day 0 to day 60.

The peak antihypertensive effect of amlodipine occurred at 5 ± 2 h after drug administration. The mean placebo-adjusted peak decrease in hourly blood pressure with amlodipine was −25 mm Hg for SBP and −14 mm Hg for DBP. There was no significant variation in heart rate in either treatment group at the time of peak effect (−1.2 ± 8 beats/min with placebo and 0.2 ± 9 beats/min with amlodipine). The percentage of ABPM responders in the amlodipine group (85.7%; 12/14) was significantly greater (\( P = .025 \)) than in the placebo group (41.2%; 7/17).

For clinic measurements, there was a significantly greater mean reduction in SBP (\( P = .01 \)) and DBP (\( P = .0007 \)), between day 0 and day 60, in patients treated with amlodipine than in those treated with placebo. Mean heart rate did not differ between the two groups at day 0, day 60, or in the change from day 0 to day 60.

Mean SBP, DBP, and RR interval were similar between the two treatment groups at day 0. At day 60, however, mean SBP was significantly lower in amlodipine-treated patients than in placebo-treated patients (131.8 ± 19.2 mm Hg vs 149.7 ± 16.7 mm Hg; \( P = .01 \)). The decrease in SBP between day 0 and day 60 was significantly greater in the amlodipine group than in the placebo group (−17.0 ± 22.0 mm Hg vs 5.7 ± 17.2 mm Hg; \( P = .004 \)). No significant differences were observed between the two groups with respect to DBP and mean RR intervals, either on day 60 or in terms of the change from day 0 to day 60.

Analysis of Baroreflex Sensitivity by Finapres

Finapres data were available for 14 amlodipine-treated patients and 17 placebo-treated patients at day 60. No statistically significant differences were seen between the treatment groups in baroreflex sensitivity at day 0 or day 60. Baroreflex sensitivity appeared to increase during the study in both groups.

Study of Blood Pressure Variability by Finapres

At day 0, the only significant differences in spectral powers between the amlodipine and placebo treatment groups were for DBP normalized spectral power in the VLF and LF bands (Table 1). In the VLF band, normalized spectral power for DBP and RR interval increased significantly in the amlodipine group, compared with placebo, between day 0 and day 60. All other changes in spectral powers in the VLF band were similar in the two treatment groups.

The LF band, between day 0 and day 60, amlodipine decreased normalized spectral powers significantly more than did placebo for SBP, DBP, and RR interval. The decrease in absolute spectral power for SBP and DBP was also significantly greater with amlodipine.

For the HF band, no statistically significant differences were observed between the amlodipine and placebo treatment groups in the changes in absolute and normalized spectral powers for SBP, DBP, or RR interval.

Adrenergic Function

Lymphocyte \( \beta _2 \)-adrenoceptor density and plasma catecholamine levels were comparable between the two treatment groups at day 0 and day 60, and in terms of the change between day 0 and day 60.

Safety Assessments

Six of the 18 patients receiving amlodipine (33.3%) and seven of the 18 patients receiving placebo (38.9%) presented with one or more adverse events during the study. The most common adverse event in the amlodipine group was leg edema, which was reported in three patients (16.7%). The most common adverse events in the placebo group were fatigue, flushing, and pharyngitis, each of which was reported in two patients (11.1%).

Discussion

This study confirms the antihypertensive efficacy of amlodipine. Twenty-four-hour ABPM and clinic blood pressure measurements showed significant decreases in SBP and DBP at day 60 with amlodipine compared with placebo. This was achieved without any effect of amlodipine on heart rate. Additionally, the percentage of responders to treatment was greater with amlodipine than with placebo.

Baroreflex sensitivity improved in both treatment groups during the study and no differences were observed between the two groups, irrespective of the time and frequency domains of the method. However, by day 60, amlodipine therapy produced an approximate 30% improvement in baroreflex sensitivity from day 0 for SBP and pulse interval sequences (\( P < .02 \)).

Spectral analysis of data from Finapres recordings demonstrated that the decrease in blood pressure with amlodipine was accompanied by a reduction in normalized spectral powers in the LF band for SBP, DBP, and RR interval and an increase in the VLF band for RR interval. A decrease in spectral power in the LF band may indicate a reduction in sympathetic activity or may reflect the interactions between the sympathetic and parasympathetic systems. However, in the current study, no changes in the total variability of the spectra for blood pressure or RR interval accompanied the decrease in the LF band, suggesting that sympathetic activity was not increased.

The difficulties in interpreting fluctuations in cardiovascular variables by means of spectral analysis of Finapres recordings are widely known. Therefore, to assist in the interpretation of our results, data on baroreflex sensitivity
<table>
<thead>
<tr>
<th>Table 1.</th>
<th>SBP, DBP, and RR interval variability at inclusion (day 0), and difference between day 0 and day 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Spectral Power, mm Hg$^2 \times 10^{-2}$ (SBP, DBP) or msec$^2$ (RR interval) [median (1st, 3rd Quartiles)]</td>
<td>Normalized Spectral Power, nu% [mean ± SD]</td>
</tr>
<tr>
<td></td>
<td>Placebo (5–10 mg) ($n = 18$)</td>
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<tr>
<td><strong>Day 0</strong></td>
<td></td>
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<tr>
<td><strong>SBP</strong></td>
<td></td>
</tr>
<tr>
<td>VLF band</td>
<td>4.8 (3.9, 8.9)</td>
</tr>
<tr>
<td>LF band</td>
<td>4.0 (2.3, 6.7)</td>
</tr>
<tr>
<td>HF band</td>
<td>1.9 (0.7, 3.1)</td>
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<tr>
<td><strong>DBP</strong></td>
<td></td>
</tr>
<tr>
<td>VLF band</td>
<td>1.8 (1.2, 3.2)</td>
</tr>
<tr>
<td>LF band</td>
<td>1.6 (1.0, 2.2)</td>
</tr>
<tr>
<td>HF band</td>
<td>0.4 (0.2, 0.9)</td>
</tr>
<tr>
<td><strong>RR interval</strong></td>
<td></td>
</tr>
<tr>
<td>VLF band</td>
<td>2.5 (0.8, 3.7)</td>
</tr>
<tr>
<td>LF band</td>
<td>1.4 (0.7, 3.2)</td>
</tr>
<tr>
<td>HF band</td>
<td>1.9 (0.6, 8.3)</td>
</tr>
<tr>
<td><strong>Difference</strong> (Day 60–Day 0)</td>
<td></td>
</tr>
<tr>
<td><strong>SBP</strong></td>
<td></td>
</tr>
<tr>
<td>VLF band</td>
<td>0.7 (−3.2, 1.8)</td>
</tr>
<tr>
<td>LF band</td>
<td>−0.3 (−1.4, 0.8)</td>
</tr>
<tr>
<td>HF band</td>
<td>−0.3 (−1.0, 0.3)</td>
</tr>
<tr>
<td><strong>DBP</strong></td>
<td></td>
</tr>
<tr>
<td>VLF band</td>
<td>0.0 (−1.4, 0.4)</td>
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<tr>
<td>LF band</td>
<td>−0.3 (−0.5, 0.2)</td>
</tr>
<tr>
<td>HF band</td>
<td>−0.3 (−0.7, 0.0)</td>
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<tr>
<td><strong>RR interval</strong></td>
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<tr>
<td>VLF band</td>
<td>−0.4 (−2.3, 0.6)</td>
</tr>
<tr>
<td>LF band</td>
<td>−0.1 (−0.7, 0.6)</td>
</tr>
<tr>
<td>HF band</td>
<td>−0.02 (−3.0, 1.3)</td>
</tr>
</tbody>
</table>

Abbreviations as in text.
and variability were analyzed in conjunction with data from other markers of sympathetic activity. The results do not indicate that there were any changes in sympathetic activity, as measured by lymphocyte \(\beta_2\)-adrenoceptor density or circulating catecholamine levels, during amlodipine treatment. These results are similar to earlier studies with amlodipine, although the designs of such studies differ.

It is recognized that sympathetic activation is not uniformly distributed across the whole cardiovascular system and that the response to dihydropyridine treatments is subject to pronounced interindividual variations.\(^1\) This may explain the relative dispersion of results and the absence of significant changes in sympathetic activity in the current study, which included only a small patient sample. In addition, the variations observed in spectral powers did not seem to be accompanied by any noticeable similar variation in baroreflex indices or the markers of sympathetic activity studied.

Results from this study suggest that amlodipine has no effect on sympathetic nervous system activity, which may be attributed to its pharmacokinetic profile. The plasma elimination half-life is 35 to 50 h and the mean time to peak concentration is 6 to 12 h after oral dosing.\(^1\) Amlodipine therefore provides a progressive and sustained antihypertensive effect with no sudden dosing-related fluctuations in blood pressure.\(^1\) This absence of sympathetic nervous system stimulation with amlodipine may be expected to have important and beneficial prognostic implications.

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**References**